Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of acute ST-segment elevation myocardial infarction

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Abstract: OBJECTIVE: To assess the cost-effectiveness of bivalirudin versus heparin and glycoprotein IIb/IIIa inhibitor (H-GPI) in patients undergoing primary percutaneous coronary intervention (PPCI) for acute ST-segment elevation myocardial infarction (STEMI), from a UK health service perspective. DESIGN: Cost-utility analysis with life-long time horizon. MAIN OUTCOME MEASURES: Costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness. METHODS: Event risks and medical resource use data derived from the HORIZONS-AMI trial were entered into a decision analytic model. Clinical events until the end of year 1 (main model) or year 3 (alternative model) were modelled in detail. Adjustments were applied to approximate UK routine practice characteristics. Life expectancy of 1-year or 3-year survivors, health-state utilities, initial hospitalisation length of stay in the comparator strategy and unit costs were based on UK sources. Costs and effects were discounted at 3.5%. RESULTS: The main model predicted bivalirudin and H-GPI patients to survive 11.52 and 11.35 (undiscounted) years on average, respectively, and to accrue 6.26 and 6.17 QALYs. Patient lifetime costs were £267 lower in the bivalirudin strategy (£12 843 vs £13 110). Extensive sensitivity and scenario analyses confirmed these results to be robust. In probabilistic analysis, quality-adjusted survival was higher and costs were lower with bivalirudin in 95.0% of simulation runs. In 99.2%, cost-effectiveness was better than £20 000 per QALY gained. Results from the alternative model were fully consistent. CONCLUSION: The use of bivalirudin instead of H-GPI in STEMI patients undergoing PPCI is cost-effective, and offers a high probability of dominance. Background treatment with aspirin and clopidogrel is assumed.

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Online Supplement

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S1 Methods - model inputs

S1.1 Long-term survival

As long-term survival data (beyond 3 years of follow-up) were not available from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, and in the absence of other suitable sources, our estimation was based on an analysis of Nottingham Heart Attack Register (NHAR) data by Palmer et al.[1] These authors estimated the average life expectancy of UK patients who survived a 6-month period after an acute coronary syndrome, with or without a non-fatal MI, to be 9.65 years. We used life-tables for England and Wales and the DEALE method to adjust this estimate for the increase in overall life expectancy since the NHAR data were collected 10-15 years ago, and for the mean age of the HORIZONS-AMI patients.[2, 3] For a diseased population of a given age, according to the DEALE method, the reciprocal of life expectancy is roughly equal to the general population mortality rate at this age plus the disease-specific excess mortality rate (m_{DS}).[2]

The population assessed by Palmer et al. had a mean age of 66 years. According to 1998-2000 life tables for England and Wales (reflecting the time when the data used by Palmer et al. were collected), life expectancy at age 66 was 17.96 years for women and 14.81 years for men [3]. Assuming one third women, as is often roughly the case in samples of cardiovascular patients, resulted in a weighted average of 15.86 years. The above-described formula hence yielded $1 / 9.65 = 1 / 15.86 + m_{DS}$, which can be solved to $m_{DS} = 0.0406$.

A general population with an average age (60.9 years) and a gender distribution as in the HORIZONS-AMI trial would have an approximate remaining life expectancy of 20.74 years, based on current (2007-2009)

life tables for England and Wales. Combining this value with the above-estimated disease-specific excess mortality, again using the DEALE formula, led to an estimated average life expectancy of the HORIZONS-AMI first-year survivors of 11.26 years.

This value was used in our main model. Here, patients entered the Markov module at year 1, while the original estimate by Palmer et al. was for six-month survivors. However, in light of potentially improved life expectancy of myocardial infarction (MI) survivors due to medical progress and shift from fibrinolysis to primary percutaneous coronary intervention (PPCI) since the NHAR data were collected, a notion supported by a recent analysis of a UK primary care database,[4] and as one-year survivors may be healthier on average than six-month survivors, no additional correction for this difference was applied.

In the alternative model, overall survival in the comparator strategy was made identical to that seen in the main model. This led to an estimated average life-expectancy of three-year survivors of 9.37 years.

S1.2 Resource use – tirofiban vials

An assumption of use of one 12.5 mg tirofiban vial, for each patient receiving tirofiban, was made. This would be consistent with a high dose strategy (25 μg/kg bolus and subsequent 0.15 μg/kg/minute infusion) as tested in the Ongoing Tirofiban in Myocardial Infarction Evaluation 2 (On-TIME 2) study.[5]

S1.3 Resource use – length of stay

In order to achieve a UK practice perspective on initial hospitalisation, length of stay in the heparin and glycoprotein IIb/IIIa inhibitor (H-GPI) strategy was assumed to be 4.4 days (compared to 7.2 days in HORIZONS-AMI), as reported for the STEMI patients receiving PPCI in the six control sites for the English National Infarct Angioplasty Project (NIAP) [6]. This value was assumed to reflect current routine practice in the UK. The relative reduction in length of stay observed in the HORIZONS-AMI bivalirudin arm was applied to the 4.4 days. As information on type of ward was only collected in HORIZONS-AMI patients enrolled in the USA, the arm-specific relative proportions of normal ward days and intensive care unit/coronary care unit (ICU/CCU) days were assessed for this sub-population and subsequently applied to the estimated length of stay in each arm. Length of stay differences by type of ward were estimated on this basis (see main publication document, Table 2). Normal ward length of stay was marginally higher in the bivalirudin strategy but ICU length of stay was reduced. In consequence, overall length of stay was reduced in the bivalirudin strategy.

Corresponding bias-corrected standard errors were estimated using bootstrap methods, as a basis for sensitivity analysis. (These standard errors and their corresponding confidence intervals do not take into account uncertainty in the length of stay assumption of 4.4 days for the H-GPI strategy.)

S1.4 Resource use – clinical events

As a basis for correct costing of diagnostic angiographies, PCI and CABG procedures, and clinical events (i.e. bleeding, ischaemic stroke, repeat MI and death), events occurring during the initial hospitalisation period were distinguished from subsequent events in order to avoid double-counting of ward days. Additional parameters distinguished Q-wave from non-Q-wave repeat MIs, and repeat revascularisations using PCI or CABG, to ensure correct modelling of resource use. A list of auxiliary model parameters is provided in Table S1.4-1, below. Due to expected marginal impact, there parameters were not varied in sensitivity analysis.

Table S1.4-1. Auxiliary model parameters

Parameter description	Value	Source
One-year-based model		
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in H-GPI strategy if radial arterial access use as seen in HORIZONS-AMI	0.612	HORIZONS-AMI 1-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in bivalirudin strategy if radial arterial access use as seen in HORIZONS-AMI	0.670	HORIZONS-AMI 1-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in H-GPI strategy if radial arterial access use is 42.5%[a]	0.733	HORIZONS-AMI 1-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in bivalirudin strategy if radial arterial access use is 42.5%[a]	0.779	HORIZONS-AMI 1-year data
Non-CABG HORIZONS-AMI minor bleed, proportion of non-access site bleeds in both strategies	0.000	Assumed for simplicity, due to marginal impact on health economic results
Repeat MIs, proportion of Q-wave MIs in H-GPI strategy	0.474	HORIZONS-AMI 1-year data
Repeat MIs, proportion of Q-wave MIs in bivalirudin strategy	0.613	HORIZONS-AMI 1-year data
Any repeat revascularisation, proportion of PCI use (versus CABG use) in H-GPI strategy	0.839	HORIZONS-AMI 1-year data
Any repeat revascularisation, proportion of PCI use (versus CABG use) in bivalirudin strategy	0.885	HORIZONS-AMI 1-year data
Repeat angiographies not leading to PCI in H-GPI strategy (mean number)	0.035	HORIZONS-AMI 1-year data

Parameter description	Value	Source
Repeat angiographies not leading to PCI in bivalirudin strategy (mean number)	0.037	HORIZONS-AMI 1-year data
Average survival time of 1-year survivors in H-GPI strategy (days)	59	HORIZONS-AMI 1-year data
Average survival time of 1-year survivors in bivalirudin strategy (days)	83	HORIZONS-AMI 1-year data
Three-year-based model		
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in H-GPI strategy if radial arterial access use as seen in HORIZONS-AMI[b]	0.638	HORIZONS-AMI 3-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in bivalirudin strategy if radial arterial access use as seen in HORIZONS-AMI[b]	0.678	HORIZONS-AMI 3-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in H-GPI strategy if radial arterial access use is 42.5%[a,b]	0.754	HORIZONS-AMI 3-year data
Non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds in bivalirudin strategy if radial arterial access use is 42.5%[a,b]	0.786	HORIZONS-AMI 3-year data
Non-CABG HORIZONS-AMI minor bleed, proportion of non-access site bleeds in both strategies	0.000	Assumed for simplicity, due to marginal impact on health economic results
Repeat MIs, proportion of Q-wave MIs in H-GPI strategy	0.466	HORIZONS-AMI 3-year data
Repeat MIs, proportion of Q-wave MIs in bivalirudin strategy	0.899	HORIZONS-AMI 3-year data
Any repeat revascularisation, proportion of PCI use (versus CABG use) in H-GPI strategy	0.867	HORIZONS-AMI 3-year data
Any repeat revascularisation, proportion of PCI use (versus CABG use) in bivalirudin strategy	0.885	HORIZONS-AMI 3-year data
Repeat angiographies not leading to PCI in H-GPI strategy (mean number)	0.071	HORIZONS-AMI 1-year data
Repeat angiographies not leading to PCI in bivalirudin strategy (mean number)	0.079	HORIZONS-AMI 1-year data
Average survival time of 3-year survivors in H-GPI strategy (days)	307	HORIZONS-AMI 3-year data
Average survival time of 3-year survivors in bivalirudin strategy (days)	343	HORIZONS-AMI 3-year data

a Assumed to represent radial arterial access use in the UK and therefore used in the base case analysis.

b The arm-specific proportion of access site bleeds vs. non-access site bleeds in years 2-3 was assumed to be the same as between day 30 and end of year 1. The information on the frequency of non-access site bleeds was used to estimate the impact of higher radial arterial access use in UK routine practice than observed in the HORIZONS-AMI trial.

CABG, coronary artery bypass graft; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; PCI, percutaneous coronary intervention.

S1.5 Unit costs

Unit costs represented 2009-10 prices. Where necessary, older unit costs were inflated using the UK Pay & Prices Index for Hospital & Community Health Services.[7]

Public drug prices were taken from the MIMS website and checked for identity with the British National Formulary.[8, 9] Ward costs and unit costs of angiography, PCI, CABG and repeat MI were primarily based on NHS reference costs for Healthcare Resource Groups (HRGs). As there were no NHS reference costs published for 2009-10, 2008-09 values [10] or, in some cases, earlier values [11, 12] served as a basis.

As cardiology ward costs might be influenced by procedure costs, the cost per day in general medicine was used as the unit cost for a normal ward day.[11] The average of the cost per day on ICU (weighted average of Currency Codes XC01Z-XC07Z representing adult critical care) and of the cost per day on CCU (Currency Code CC7) was used to represent the unit cost for an ICU/CCU day, as the HORIZONS-AMI study did not distinguish between the two.[10]

HRG RBF2 represented the procedure cost of angiography[12], HRG EA32Z the cost of PCI,[10] HRG EA16Z the cost of CABG surgery,[10] and HRG EB10Z (for MI without complications) the cost of Q-wave MI.[10] Average HRG costs, weighted by case number, of elective and non-elective cases were used as applicable. Additional distinctions (e.g. between non-elective short stay and non-elective long-stay cases) were taken into account in the same way. Non-Q-wave MIs occurring after the initial hospitalisation were assumed to cost 31% of a Q-wave MI.[13] The cost of ischaemic stroke was represented by the first year cost of stroke treatment estimated by Bravo Vergel et al.[14]

For procedures and events during the initial hospitalisation period, ward costs were excluded in order to avoid double counting. We assumed a non-ward cost proportion of 55% for PCI[15] and a cost proportion of 30% incurred in theatre in cardiac surgery for CABG.[16] For ischaemic strokes occurring during the initial hospitalisation, the overall estimate was reduced by 80% of the cost of HRG AA22Z,[10] which was assumed to mostly represent ward costs. The non-ward costs of MIs during the initial hospitalisation were assumed to be covered by angiography, PCI and CABG costs.

There are no published bottom-up data quantifying the costs of MI treatment-related or PCI-related bleedings but it is clear that their cost impact is partially due to their influence on length of stay.[17] We covered this element by modelling initial hospitalisation ward costs. However, additional costs for bleeding-induced examinations and procedures are expected and some bleeds occurred after the initial hospitalisation. The additional examination and procedure costs of HORIZONS-AMI major bleedings,[18] and their full costs, were estimated to be 75% of the procedure and full costs of a repeat PCI, respectively.[19, 20] The value of 75% was

based on published regression analyses of the impact of bleedings and other events on the costs of cardiovascular hospital admissions. Cohen et al. performed such an analysis for the US patients enrolled in the REPLACE-2 trial.[19] They estimated the cost impact of a major per-protocol bleed and a repeat PCI to be USD 6,300 and USD 8,187, respectively. Pinto et al. performed a similar analysis for the ACUITY trial and reported estimates of USD 8,658 and USD 12,293 for major per-protocol bleeds and unplanned PCI or CABG.[20] The estimate of 75% is also supported or at least not contradicted by some other publications.[17, 21-23] Transfusion costs were not added, in order to avoid double-counting. HORIZONS-AMI minor bleedings were assumed to cost 6% of a major bleeding.[19]

Long-term annual cardiovascular treatment costs after the first year (or after the first three years, in the alternative model) were estimated from a published model of thrombolysis versus primary PCI in MI patients[24] that also served as a basis for a cost-effectiveness analysis alongside the NIAP project reported by Goodacre et al.[6] Bravo Vergel et al. showed how the remaining life-time of 6-month MI survivors is distributed between a well state (indicating that no further MI or stroke events occurred after the initial MI), a repeat MI state and a stroke state. For both types of events, first year costs and costs accrued in each subsequent year were distinguished. In the absence of precise information, we applied the first year costs to one third of the time spent in the repeat MI and stroke states, respectively. We combined the resulting information with annualised health state costs (based on 2003/04 prices) as provided in Table 15 of the Bravo Vergel et al. report, and adjusted for inflation. This resulted in an approximation of the annual long-term cardiovascular treatment costs of STEMI survivors, taking into account the costs of repeat MIs and strokes on a summary basis.

S2 Methods – scenario analyses

S2.1 Tentative set of UK-based comparator strategy event risks

For a scenario analysis, HORIZONS-AMI-based one-year event risks in the comparator strategy were replaced with a tentative set of UK-based one-year event risks compiled from different sources. Myocardial Ischaemia National Audit Project (MINAP) data on patients with unstable angina or non-STEMI and undergoing PCI provided a bleeding risk estimate of 2.1%, much lower than that seen in HORIZONS-AMI.[25:p.260] (It was unclear whether this discrepancy reflected an actual risk difference, which might be due to non-comparable patient or treatment characteristics, or merely differences in the reporting process and definitions used. Given definitions provided, we assumed that MINAP minor bleedings would have counted as HORIZONS-AMI major bleedings. Presumably, MINAP bleeding risks were for the initial hospitalization period and not for the first year but as most bleeding events occur in this early period, we did not adjust for this discrepancy.) The length of stay difference between strategies was adjusted to reflect the reduced bleeding risk. The one-year risk of suffering a repeat MI after the initial event was left unchanged at 4.2%.[25:p.258] Based on an extrapolation of BCIS data, the one-year risks of ischaemic stroke and repeat revascularization were reduced by half, to 0.5% and 4.3%, respectively.[26] The mortality risk of UK STEMI patients undergoing PPCI appeared to be roughly twice as high as in the HORIZONS-AMI H-GPI arm.[26, 27] The risk of death in the first year was hence increased to a NIAP-based value of 8.7%.[27]

S2.2 Scenario analyses not mentioned in the main publication document

Some scenario analyses are not mentioned in the main publication document due to space limitations: The frequency of GPI use in the bivalirudin strategy was reduced from 7.6% to 7.2% as reported in the primary HORIZONS-AMI publication[18] and increased to 13.3%, reflecting any use in the HORIZONS-AMI bivalirudin arm. The assumption of use of one 12.5 mg vial per patient receiving tirofiban was replaced with an alternative assumption of 1.5 vials. Given uncertainty around the costs of bleeding, the non-ward costs of non-CABG HORIZONS-AMI major bleedings were assumed to be no higher than transfusion costs. While no utility impact of major bleedings was modelled in the base case analysis due to lack of data, a life-long utility decrease of 0.05 was introduced to reflect a possible long-term impact. Initial hospitalisation length of stay in the comparator strategy was assumed to be 7.2 days as observed in the HORIZONS-AMI trial.

S3 Sensitivity analysis results

Table S3-1. Deterministic sensitivity analysis of main model results, exploring the impact of statistical uncertainty. (In the main model detailed modelling of clinical events covered the time period from the initial STEMI event to end of year 1)

Varied parameter	Favours H-GPI strategy		Favours bivalirudin strategy	
	Varied parameter values	ICER (£ per QALY gained)	Varied parameter values	ICER (£ per QALY gained)
Base case	Bivalirudin dominant; Δ cost £-267 and Δ QALY 0.089, per patient			
Comparator strategy risk of non-CABG HORIZONS-AMI major bleeding[a]	6.5%	Dominant; Δ cost £-262	9.0%	Dominant; Δ cost £-273
Comparator strategy risk of non-CABG HORIZONS-AMI minor bleeding[a]	6.9%	Dominant; Δ cost £-267	9.5%	Dominant; Δ cost £-268
Comparator strategy risk of ischaemic stroke / repeat MI / repeat revascularisation[a]	1.6% / 5.3% / 10.0%	Dominant; Δ cost £-264	0.6% / 3.3% / 7.3%	Dominant; Δ cost £-270
Comparator strategy risk of death[a]	3.8%	Dominant; Δ cost £-290; Δ QALY 0.071[b]	5.9%	Dominant; Δ cost £-241; Δ QALY 0.111[b]
Relative risk of non-CABG HORIZONS-AMI major bleeding in bivalirudin strategy[a]	0.823	Dominant; Δ cost £-247	0.497	Dominant; Δ cost £-284
Relative risk of non-CABG HORIZONS-AMI minor bleeding in bivalirudin strategy[a]	0.692	Dominant; Δ cost £-266	0.454	Dominant; Δ cost £-268
Relative risk of ischaemic stroke / repeat MI / repeat revascularisation in bivalirudin strategy[a]	2.007 / 1.135 / 1.381	Dominant; Δ cost £-93	0.556 / 0.588 / 0.914	Dominant; Δ cost £-382
Relative risk of death in bivalirudin strategy[a]	0.979	Dominant; Δ cost £-369; Δ QALY 0.008[b]	0.515	Dominant; Δ cost £-193; Δ QALY 0.148[b]
Life expectancy of 1st year survivors	8.45	Dominant; Δ cost £-286; Δ QALY 0.074[b]	14.08	Dominant; Δ cost £-251; Δ QALY 0.102[b]
Utility decrement, first year / subsequent years	0.396 / 0.353	Dominant; Δ QALY 0.08	0.238 / 0.212	Dominant; Δ QALY 0.10
Index hospitalisation normal ward / ICU length of stay (H-GPI)	2.28 / 1.76	Dominant; Δ cost £-248	2.65 / 2.16	Dominant; Δ cost £-288
Difference in index hospitalisation normal ward / ICU length of stay (Δ bivalirudin – H-GPI)	0.33 / 0.00	Dominance lost; ICER £415 per QALY gained (Δ cost £ 37; Δ QALY 0.089)	-0.21 / -0.49	Dominant; Δ cost £-523
Cost of cardiovascular outpatient treatment and drugs in year 1	1,350	Dominant; Δ cost £-261	450	Dominant; Δ cost £-273
Annual long-term cardiovascular treatment cost of STEMI survivors	1,350	Dominant; Δ cost £-217	450	Dominant; Δ cost £-317
No. of bivalirudin 250 mg vials under bivalirudin strategy	1.26	Dominant; Δ cost £-259	1.21	Dominant; Δ cost £-274

Varied parameter	Favours H-GPI strategy		Favours bivalirudin strategy	
	Varied parameter values	ICER (£ per QALY gained)	Varied parameter values	ICER (£ per QALY gained)
No. of abciximab 10 mg vials and eptifibatide 20 mg / 75 mg vials in bivalirudin strategy[c]	2.96 / 1.78 / 2.75	Dominant; Δ cost £-265	2.63 / 1.50 / 2.26	Dominant; Δ cost £-270
No. of abciximab 10 mg vials and eptifibatide 20 mg / 75 mg vials in H-GPI strategy[c]	3.03 / 1.84 / 2.17	Dominant; Δ cost £-260	3.11 / 1.92 / 2.30	Dominant; Δ cost £-274
Angiography procedure cost	501	Dominant; Δ cost £-267	269	Dominant; Δ cost £-267
PCI cost / PCI procedure cost	3,865 / 2,126	Dominant; Δ cost £-261	2,278 / 1,253	Dominant; Δ cost £-275
CABG cost / CABG procedure cost	6,690 / 2,489	Dominant; Δ cost £-264	9,707 / 3,611	Dominant; Δ cost £-269
Q-wave MI cost / non-Q-wave MI cost	1,291 / 400	Dominant; Δ cost £-265	2,011 / 623	Dominant; Δ cost £-269
Stroke cost / stroke cost excluding ward cost of initial hospitalisation	15,917 / 13,309	Dominant; Δ cost £-265	5,306 / 4,436	Dominant; Δ cost £-270
Non-CABG HORIZONS-AMI major bleeding cost / non-CABG HORIZONS-AMI major bleeding procedure cost	1,182 / 650	Dominant; Δ cost £-250	3,545 / 1,950	Dominant; Δ cost £-284
Non-CABG HORIZONS-AMI minor bleeding cost / non-CABG HORIZONS-AMI minor bleeding procedure cost	72 / 40	Dominant; Δ cost £-266	216 / 119	Dominant; Δ cost £-269

a Index hospitalisation length of stay was averaged within strategies, and not modelled event specific, as this would have inflated statistical uncertainty. In consequence, any influence of clinical events on the initial hospitalisation length of stay difference between strategies is not covered here but on a summary basis in separate sensitivity analyses of length of stay parameters.

b Categorisation as favouring the H-GPI strategy, or the bivalirudin strategy, was arbitrary in this particular case as the cost advantage and the QALY gain shifted in opposite directions.

c Numbers of 20 mg vials and 75 mg vials were assessed separately. For the purpose of modelling, the number of 20 mg vials was then converted into 75 mg vials, taking into account the price difference per mg of substance between the two vial sizes.

CABG, coronary artery bypass graft; CCU, coronary care unit; Δ, difference calculated by subtracting value for H-GPI strategy from value for bivalirudin strategy; GPI, glycoprotein IIb/IIIa inhibitor; H-GPI, heparin and glycoprotein IIb/IIIa inhibitor; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention; QALY, quality-adjusted life year.

Figure S3-1. **Probabilistic sensitivity analysis of alternative model results, exploring the impact of statistical uncertainty. (In the alternative model detailed modelling of clinical events covered the time period from the initial STEMI event to end of year 3.) The bivalirudin strategy was dominant (i.e. was cost-saving and showed a QALY gain) in 9,322 (93.2%) of 10,000 model runs. The cost-effectiveness threshold of £20,000 per QALY gained was met in 9,934 (99.3%) of 10,000 runs.**

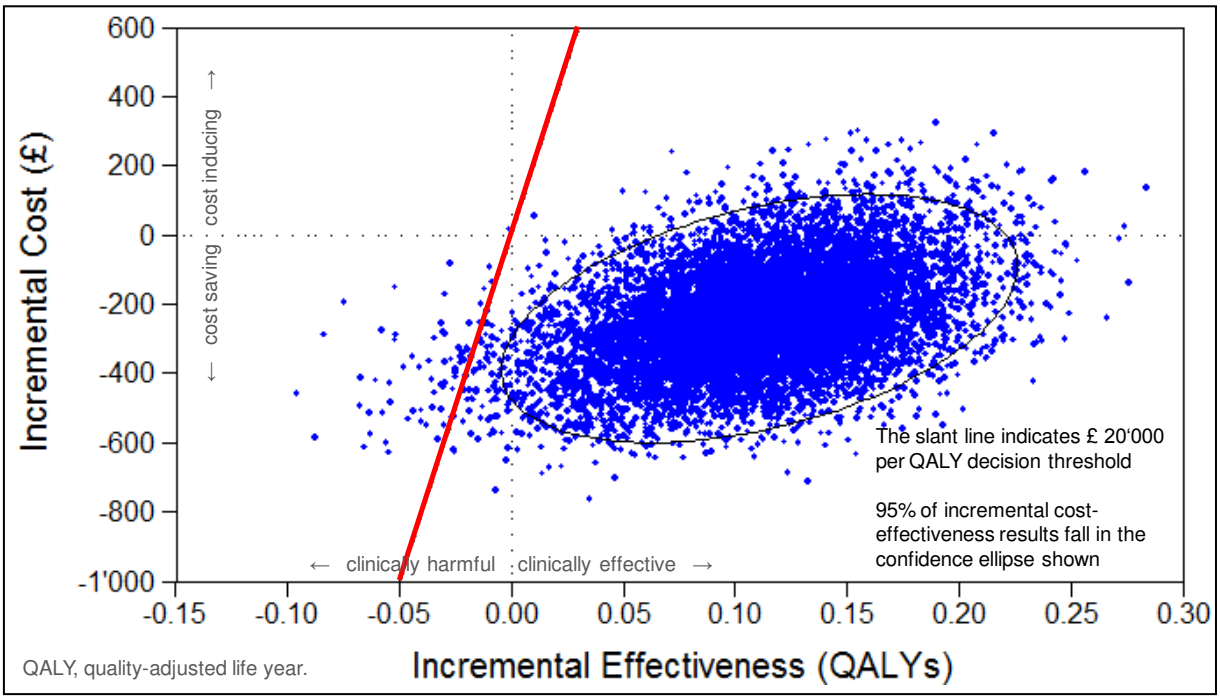

Table S3-2. Scenario analysis of main model results. (In the main model detailed modelling of clinical events covered the time period from the initial STEMI event to end of year 1.)

Varied parameters	Favours H-GPI strategy		Favours bivalirudin strategy	
	Varied parameter values	ICER (£ per QALY gained)	Varied parameter values	ICER (£ per QALY gained)
Base case	Bivalirudin dominant; Δ cost £-267 and Δ QALY 0.089, per patient			
One-year event risks in H-GPI strategy				
Non-CABG HORIZONS-AMI major bleeding Ischaemic stroke Repeat MI Any repeat revascularisation Death	--	--	2.1%[a] 0.5% 4.2% 4.3% 8.7%	Dominant; Δ cost £-21; Δ QALY 0.163[b]
Anticoagulant use				
GPI use in bivalirudin strategy	13.3%	Dominant; Δ cost £-236	7.2%	Dominant; Δ cost £-269
Type of GPI used	(1) Abciximab 52.9%; eptifibatide 47.1% (2) Eptifibatide 100%	Dominant; Δ cost £-145 Dominance lost; ICER £1,764 per QALY gained (Δ cost £ 158; Δ QALY 0.089)	Abciximab 100%	Dominant; Δ cost £-415
In patients with tirofiban, per-patient use of tirofiban	--	--	1 vial in 50% of patients, 2 vials in the remaining 50%	Dominant; Δ cost £-281
Bleeding events				
Assume non-CABG HORIZONS-AMI major bleed non-ward costs to be equal to transfusion costs	Blood product use as observed in HORIZONS-AMI[c]	Dominant; Δ cost £-239	--	--
Long-term utility impact of major bleed	--	--	Life-long decrease by 0.05	Dominant; Δ QALY 0.101
Use and impact of arterial access				
Assume different levels of use of radial arterial access[d]	Radial arterial access, 100%	Dominant; Δ cost £-184	Radial arterial access as in HORIZONS-AMI (5.9%)	(2) Dominant; Δ cost £-329
Assume different levels of use of radial arterial access and reduced mortality difference between strategies[d,e]	(1) Radial arterial access, 42.5%[b] (2) Radial arterial access, 100%	Dominant; Δ cost £-282; Δ QALY 0.078 Dominant; Δ cost £-220; Δ QALY 0.061	--	--
Index hospitalisation length of stay and cost				
Assume index hospitalisation length of stay in H-GPI strategy to be 7.2 days as observed in HORIZONS-AMI	--	--	LOS in H-GPI strategy set to 7.2 days	Dominant; Δ cost £-391
Assume index hospitalisation length of stay to be equal in both arms	Length of stay set to equal	Dominant; Δ cost £-73	--	--

Varied parameters	Favours H-GPI strategy		Favours bivalirudin strategy	
	Varied parameter values	ICER (£ per QALY gained)	Varied parameter values	ICER (£ per QALY gained)
Combined				
Assume 100% eptifibatide use (in patients receiving a GPI); 100% radial arterial access use with reduced bleeding; no difference in index hospitalisation length of stay	See left column	Dominance lost; ICER £4,106 per QALY gained (Δ cost £ 367; Δ QALY 0.089)	--	--
Assume 100% eptifibatide use (in patients receiving a GPI); 100% radial arterial access use and reduced mortality difference between strategies; no difference in index hospitalisation length of stay	See left column	Dominance lost; ICER £5,428 per QALY gained (Δ cost £ 332; Δ QALY 0.061)	--	--
Discounting				
Discounting	6%	Dominant; Δ cost £-283; Δ QALY 0.077[b]	0%	Dominant; Δ cost £-232; Δ QALY 0.118[b]

a The length of stay difference between strategies was adjusted accordingly, following similar principles as described in footnote d for changes in the use of radial arterial access.

b Categorisation as favouring the H-GPI strategy, or the bivalirudin strategy, was arbitrary in this particular case as the cost advantage and the QALY gain shifted in opposite directions.

c Mean transfusion use in patients with non-CABG HORIZONS-AMI major bleeding was red blood cell units (PRBC or whole blood or other), 1.284; platelets units, 0.172; fresh frozen plasma units, 0.142. Unit costs were,[28] red blood cells, 1 bag of standard red cells, £139.72; platelets, 1 bag of platelets (1.0 ATD), £ 232.29; fresh frozen plasma, 1 bag of clinical FFP (250/300 mls UK sourced), £36.33.

d It was assumed that there were no access site bleedings in patients with radial arterial access. The occurrence of non-access site bleedings was assumed to be unaffected. In consequence, increased use of radial access led to smaller absolute risk differences for non-CABG HORIZONS-AMI major bleedings and minor bleedings. The reduced risk difference for major bleedings was assumed to lead to a proportional reduction in the length of stay difference between the bivalirudin and H-GPI strategies. This allowed to estimate the impact of different levels of use of radial access.

e Assumptions described in footnote d were maintained. The mortality difference between treatment strategies was additionally assumed to be due to major bleeding avoidance, in its entirety. The mortality increase associated with major access-site bleeding was assumed to be half of the increase associated with major non-access-site bleeding.[29, 30]

CABG, coronary artery bypass graft; Δ, difference calculated by subtracting value for H-GPI strategy from value for bivalirudin strategy; GPI, glycoprotein IIb/IIIa inhibitor; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

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